25 September 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News – S&T Supplement

1. PROTECTIVE EFFECT OF TOLL-LIKE RECEPTOR 4 IN PULMONARY VACCINIA INFECTION: *"These data establish that TLR4 mediates a protective innate immune response against vaccinia virus, which informs development of new vaccines and therapeutic agents targeted against poxviruses."*

2. PROTEOMIC ANALYSES OF FUSARIUM GRAMINEARUM GROWN UNDER MYCOTOXIN-INDUCING CONDITIONS: *"These will provide leads in the search for mechanisms and markers of host invasion and novel antifungal targets."*

3. VACCINE SAFETY ADVOCATES WANT CLARIFICATION OF FDA'S ANIMAL RULE: *"Vaccine safety advocates say FDA's new concept paper clarifying how animal studies can be used in rare situations to show the efficacy of human drugs leaves several questions unanswered, chiefly with regard to licensure requirements and how studies can gauge genetic differences between humans and animals. But an FDA official downplays the concerns."*

4. OLIGOMERIZATION OF PCRV AND LCRV, PROTECTIVE ANTIGENS OF PSEUDOMONAS AERUGINOSA AND YERSINIA PESTIS: *"The detailed understanding of structure-function relationships of T3SS needle tip proteins will be of value in further developments of new vaccines and antimicrobials."*

5. FILLING THE ANTIBIOTIC GAP: *"Research teams in Britain and Japan have come up with two new ideas to shore up modern medicine's increasingly creaky defences against bacterial diseases."*

6. ASSOCIATED PRESS EXAMINES DRUG DISPOSAL PRACTICES OF HOSPITALS, LONG-TERM CARE FACILITIES: *"Hospitals, hospices and nursing homes dump at least 250 million pounds of unused medications and contaminated packaging into the U.S. drinking water supply each year, according to an ongoing Associated Press investigation."*

7. TUBERCULOSIS POSES SECURITY THREAT IN RUSSIA, OFFICIAL SAYS:
"Tuberculosis poses a threat to Russia's security and labor force, Mikhail Grishankov, first deputy chair of the security committee of the State Duma, said recently during a roundtable

at the World Bank office in Moscow, ITAR-TASS World Service reports."

CB Daily Report

Chem-Bio News

PROTECTIVE EFFECT OF TOLL-LIKE RECEPTOR 4 IN PULMONARY VACCINIA INFECTION
By Martha A. Hutchens, Kathryn E. Luker, Joanne Sonstein, Gabriel Núñez, Jeffrey L. Curtis, Gary D. Luker
PLoS Pathogens
September 19, 2008

"Innate immune responses are essential for controlling poxvirus infection. The threat of a bioterrorist attack using Variola major, the smallpox virus, or zoonotic transmission of other poxviruses has renewed interest in understanding interactions between these viruses and their hosts. We recently determined that TLR3 regulates a detrimental innate immune response that enhances replication, morbidity, and mortality in mice in response to vaccinia virus, a model pathogen for studies of poxviruses. To further investigate Toll-like receptor signaling in vaccinia infection, we first focused on TRIF, the only known adapter protein for TLR3. Unexpectedly, bioluminescence imaging showed that mice lacking TRIF are more susceptible to vaccinia infection than wild-type mice. We then focused on TLR4, the other Toll-like receptor that signals through TRIF. Following respiratory infection with vaccinia, mice lacking TLR4 signaling had greater viral replication, hypothermia, and mortality than control animals. The mechanism of TLR4-mediated protection was not due to increased release of proinflammatory cytokines or changes in total numbers of immune cells recruited to the lung. Challenge of primary bone marrow macrophages isolated from TLR4 mutant and control mice suggested that TLR4 recognizes a viral ligand rather than an endogenous ligand. These data establish that TLR4 mediates a protective innate immune response against vaccinia virus, which informs development of new vaccines and therapeutic agents targeted against poxviruses."

The full article can be found at: http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000153;jsessionid=5AC01A3B3749A810CA368E6E2F077F75

Return to Top

PROTEOMIC ANALYSES OF FUSARIUM GRAMINEARUM GROWN UNDER MYCOTOXIN-INDUCING CONDITIONS
Biotech Law Weekly
September 19, 2008

"Non-gel-based quantitative proteomics technology was used to profile protein expression differences when Fusarium graminearum was induced to produce trichothecenes in vitro. As F. graminearum synthesizes and secretes trichothecenes early in the cereal host invasion

process, we hypothesized that proteins contributing to infection would also be induced under conditions favouring mycotoxin synthesis. Protein samples were extracted from three biological replicates of a time course study and subjected to iTRAQ (isobaric tags for relative and absolute quantification) analysis."

“Statistical analysis of a filtered dataset of 435 proteins revealed 130 F. graminearum proteins that exhibited significant changes in expression, of which 72 were upregulated relative to their level at the initial phase of the time course. There was good agreement between upregulated proteins identified by 2-D PAGE/MS/MS and iTRAQ. RT-PCR and northern hybridization confirmed that genes encoding proteins which were upregulated based on iTRAQ were also transcriptionally active under mycotoxin producing conditions. Numerous candidate pathogenicity proteins were identified using this technique."

“These will provide leads in the search for mechanisms and markers of host invasion and novel antifungal targets."

The full article can be found at: (R.D. Taylor, et. al., “Proteomic analyses of Fusarium graminearum grown under mycotoxin-inducing conditions”. Proteomics, 2008;8(11):2256-2265). Link not available.

Return to Top

VACCINE SAFETY ADVOCATES WANT CLARIFICATION OF FDA'S ANIMAL RULE
FDA Week
September 19, 2008

“Vaccine safety advocates say FDA's new concept paper clarifying how animal studies can be used in rare situations to show the efficacy of human drugs leaves several questions unanswered, chiefly with regard to licensure requirements and how studies can gauge genetic differences between humans and animals. But an FDA official downplays the concerns.

The advocates are particularly concerned by the paper's suggestion that a drug could be studied in only one animal species, as opposed to two as called for by the animal rule, and that animal pharmacokinetic studies might substitute for some human safety data.”

“FDA has done a good job of pointing out how animal data that show efficacy have in the past not been translatable to humans; that the usefulness of animal models can be muddied by differences between humans and animals in time of onset; disease progression; disease manifestations; problems in establishing the correct dose, etc.," physician and vaccines expert Meryl Nass states in an e-mail.

"However, after an excellent explication of these complex issues, very little light was shed on specifically how to avoid these pitfalls, except that sponsors should consult early with FDA," says Nass, who has testified at several congressional hearings on vaccines, particularly anthrax.

Of particular concern to Nass is the paper's statement that efficacy might only need to be demonstrated in one animal species. The statement is made "without any explanation of why only one species would be sufficient, when the Animal Rule asks for two," she says.

She adds: "Another specific part of the guidance deals with FDA's understanding that some experimental animals have limited availability, suggesting that data from small numbers of animals will be acceptable in some cases."

Link not available.

Return to Top

OLIGOMERIZATION OF PCRV AND LCRV, PROTECTIVE ANTIGENS OF PSEUDOMONAS AERUGINOSA AND YERSINIA PESTIS
Health Risk Factor Week
September 23, 2008

"Protective antigens of Pseudomonas aeruginosa (PcrV) and Yersinia pestis (LcrV) are key elements of specialized machinery, the type III secretion system (T3SS), which enables the injection of effector molecules into eukaryotic cells. Being positioned at the injectisome extremity, V proteins participate in the translocation process across the host cell plasma membrane."

"In this study, we demonstrate the assembly of V proteins into oligomeric doughnut-like complexes upon controlled refolding of the proteins in vitro. The oligomeric nature of refolded PcrV was revealed by size exclusion chromatography, native gel electrophoresis, and native mass spectrometry, which ascertain the capacity of the protein to multimerize into higher-order species. Furthermore, transmission electron microscopy performed on oligomers of both PcrV and LcrV revealed the presence of distinct structures with approximate internal and external diameters of 3-4 and 8-10 nm, respectively. The C-terminal helix, alpha12, of PcrV and notably the hydrophobic residues Val(255), Leu(262), and Leu(276) located within this helix, were shown to be crucial for oligomerization. Moreover, the corresponding mutant proteins produced in P. aeruginosa were found to be non-functional in in vivo type III-dependent cytotoxicity assays by directly affecting the correct assembly of PopB/D translocon within the host cell membranes."

"The detailed understanding of structure-function relationships of T3SS needle tip proteins will be of value in further developments of new vaccines and antimicrobials."

The full article can be found at: (G. Caroline, et. al., “Oligomerization of PcrV and LcrV, protective antigens of Pseudomonas aeruginosa and Yersinia pestis”. Journal of Biological Chemistry, 2008;283(35):23940-9). Link not available.

Return to Top

FILLING THE ANTIBIOTIC GAP
By John Bonner
Chemistry World
September 19, 2008

“Research teams in Britain and Japan have come up with two new ideas to shore up modern medicine's increasingly creaky defences against bacterial diseases.”

“But at the same time as the old antibiotics are losing their effectiveness, the supply of new drugs is drying up, with only two new classes of antibacterials having been developed during the past 30 years.”

“Working with colleagues at universities in the UK and India, Prolysis Ltd researchers have discovered a small molecule that inhibits the function of a protein called FtsZ. This protein plays a key role in bacterial cell division, polymerising to form a ring that eventually forms the wall dividing the two daughter cells. Several small molecules have previously been shown to have in vitro activity against FtsZ, but none has worked so far in a live animal. David Haydon and his colleagues systematically modified 500 analogues of one such compound, 3-methoxybenzamide, until they found the candidate drug - called PC190725, the inhibitor combines a benzamide with thiazolopyridine through an ether linkage. This compound was given to mice infected with a normally lethal dose of MRSA, and every one survived.”

The full article can be found at: http://www.rsc.org/chemistryworld/News/2008/September/19090802.asp

Return to Top

TUBERCULOSIS POSES SECURITY THREAT IN RUSSIA, OFFICIAL SAYS

News-Medical.net
September 24, 2008

“Tuberculosis poses a threat to Russia's security and labor force, Mikhail Grishankov, first deputy chair of the security committee of the State Duma, said recently during a roundtable at the World Bank office in Moscow, ITAR-TASS World Service reports.”

“According to Grishankov, "social infections" such as TB and HIV "pose a real threat" to Russia's security because they often affect people during their prime working years, at a time when the country is experiencing a labor shortage. In addition, drug-resistant TB is increasing in Russia and requires more expensive treatment than drug-sensitive strains of the disease.”

The full article can be found at: http://www.news-medical.net/?id=41649

Return to Top

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